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(54) PROCESS FOR PREPARING SUBSTITUTED PHENYLALKANOIC ACIDS AND INTERMEDIATES

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ABSTRACT:

CLAIMS: Show all claims

*** Note: Data on abstracts and claims is shown in the official language in which it was submitted.

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(72) Inventors (Country): **SLETZINGER, MEYER** (Not Available)
WILDMAN, ARTHUR S. (JR.) (Not Available)
ALLEGRETTI, JOHN E. (Not Available)

(73) Owners (Country): **MERCK AND CO.** (Not Available)

(71) Applicants (Country):

(74) Agent:

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PROCESS FOR PREPARING SUBSTITUTED PHENYLALKANOIC ACIDS AND INTERMEDIATES

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Inventor:	ALLEGRETTI JOHN E; SLETZINGER MEYER; WILDMAN ARTHUR S JR
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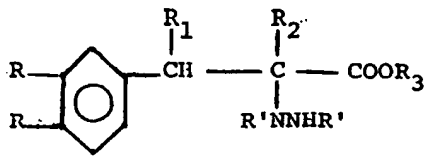
This invention provdes a new method for preparing the optical isomers of certain α-hydrazino-β-phenylalkanoic acids. More particularly, it provides a new method for preparing α-hydrazino-β-hydroxyphenyl alkanoic acids in substantially pure form.

It is known in the art that various α-hydrazino-β-phenylalkanoic acids are useful as decarboxylase inhibitors. It is further known that the D-isomer of these acids is generally inactive and may even be antagonistic to the action of the L-form, thereby reducing its potency.

In the past, it has been the accepted practice to separate stereoisomers by the formation of diastereomeric salts with either optically active bases or acids, depending on the nature of the racemate. However, with the hydrazino compounds of the present invention, separation is complicated by the fact that some diastereomeric salts do not form crystalline materials with sufficiently different properties so that the diastereomers can be readily crystallized. In some instances, the diastereomeric salts are oily or waxy materials which become difficult if not impossible to separate by conventional means. Quite obviously, if a relatively simple and inexpensive process could be found which would preferentially produce the desired L-α-hydrazino-β-phenylalkanoic acids, it would receive widespread acceptance in the art.

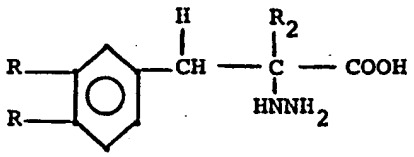
This invention provides the optical enantiomorphs in substantially pure form of a compound of Formula I:



I

where
R is hydrogen,
hydroxy,
loweralkyloxy,
arloweralkyloxy or
acyloxy (preferably acetyloxy, formyloxy, trifluoroacetyloxy or benzoyloxy);
R_1 and R_2 are hydrogen or
lower alkyl;
R_3 is hydrogen or
lower alkyl; and
R' is hydrogen or
acyl (preferably acetyl, formyl, trifluoroacetyl or benzoyl);
by subjecting a supersaturated aqueous solution of the racemic mixture with crystalline seed of the desired racemate.

A more preferred embodiment of this invention describes the preparation of the L-stereoisomeric compounds of Formula II:



II

where

R and R_2 are as described above.

It is to be understood that the L-configuration is in reference to the absolute configuration on the α-carbon in relation to the hydrazine.

A most preferred embodiment of this invention describes the preparation of L-α-(3,4-dihydroxybenzyl)-α-hydrazino propionic acid and L-β-(3,4-dihydroxyphenyl)-α-hydrazino propionic acid.

The "lower alkyl" radical signifies an alkyl group containing from 1 to about 6 carbon atoms which can be straight chained or branched.

The "lower alkoxy" radical signifies an alkoxy group containing from 1 to about 6 carbon atoms which can be straight chained or branched.

"Aralkoxy" refers to an arylalkoxy group, the aryl portion of which may be one or more phenyl or naphthyl radicals attached to an alkoxy radical which contains from 1 to about 3 carbon atoms. The preferable aralkoxy groups are benzyl, diphenylmethyl, trityl and naphthylmethyl.

We have found that it is possible to selectively crystallize a specific enantiomorph of a compound of Formula I from a racemic mixture of this compound.

We have found that this selective crystallization directly results in substantially pure enantiomorph.

We have also found that it is possible to carry out this direct crystallization by a continuous method, thus providing efficient methods for obtaining large quantities of desired enantiomorph.

To practice the present invention the racemic mixture of the compound of Formula I is dissolved in an aqueous solution containing from 0 to 90% of an acid capable of forming a salt, thus resulting in the amine salt of this acid in the same proportions that is 0 to 90%. The mixture now exists as a supersaturated solution. This supersaturated solution is then subjected with one enantiomorph which is in crystalline form and a direct crystallization occurs. The resolved enantiomorph is then separated from the mother liquor and the mother liquor is further subjected to the other enantiomorph to again obtain a direct crystallization.

It is preferred that a saturated solution of the racemic mixture be prepared at 60-100°C. in the solvent which contains a small amount of the acid capable of forming the salt. A saturated solution results having from 0 to 20% of the racemic mixture in the salt form. This ratio is controlled by the amount of compound added. The saturated solution is then filtered, the filtrate seeded with the desired enantiomorph and then cooled to 5 to 40°C.

This invention further provides for continuous methods of operating this direct crystallization. This is accomplished by taking the mother liquor from the second direct crystallization above and using this to dissolve the racemic mixture. The resolved enantiomorphs are withdrawn at each stage of the resolution.

A further continuous method is accomplished by dissolving the racemic mixture in aqueous solution containing some acid as above. This is then divided into two parts and each part is subjected to one enantiomorph. After the

crystallized enantiomorphs are isolated the mother liquors are used in the dissolving step of the unisolated enantiomorph.

The acids which may be used to form the salts should be one that is water soluble. It is preferred that they be non-oxidizing to the hydroxyl groups present since those groups are sensitive to oxidation to the quinonyl compounds. It is further preferred that the acids be one which have at least one acidic hydrogen with an ionization constant greater than 10^{-3}. This ionization constant is preferable in order to provide an acid which will readily form the desired salt of the hydrazine when more than very small amounts of acid are used. When only small amounts of acid are used any acid soluble in the solvent may be used. Acids that may preferably be used include such as:

hydrochloric acid;
hydrobromic acid;
sulfuric acid;
sulfurous acid;
monochloroacetic acid;
dichloroacetic acid;
trichloroacetic acid and
substituted phosphonic acids.

Other acids that may be used but are less preferred include such as:

acetic acid;
dilute nitric acid;
perhalocarboxylic acids;
perchloric acid;
polyhalocarboxylic acids;

alkyl or aryl sulfonic acids;

hydro and monoalkyl sulfates;

phosphoric acid derivatives;

strong acid-type resins; or

sulfonic acid resins.

The process of this invention may further be carried out in the absence of acid. Thus, for example, a supersaturated aqueous solution of the hydrazino-acid may be prepared and upon seeding the desired enantiomorph results.

The solvent medium used in this invention should be one in which the acid and the racemic mixture is soluble. It is preferable that the solvent of this invention be a polar solvent and most preferably an aqueous solvent containing at least 10% water by volume. Water itself is most preferred, however, representative solvents which can be used include such as:

formic acid;

acetic acid;

propionic acid, etc.;

dioxane;

acetone;

methylethylketone;

diethylketone, etc.;

methanol;

ethanol;

propanol;

isopropanol, etc.;

diethyleneglycol monomethylether;

diethyleneglycol monobutylether, etc.;

ethyleneglycol dimethylether;

ethyleneglycol monomethylether, etc.;

diethyleneglycol;

triethyleneglycol; and

tetrahydrofuran, etc.

The supersaturated solutions of this invention may be prepared by changing solubility with temperature. Thus, for example, a saturated solution may be formed at one temperature and cooled. Since the solubility is less at a lower temperature the saturated solution becomes supersaturated at the lower temperature. It is preferred to prepare a saturated solution at one temperature and cool in the presence of the seeding crystals to a lower temperature. Thus, it is desirable to dissolve the racemic mixture at temperatures between 40° and 100°C. and to form the supersaturated solution by cooling to temperatures between 5 and 40°C. It is most preferred to form the saturated solution at about 75°C.

The greater the difference between the temperature of forming the saturated solution and the temperature at which the supersaturated solution is used for the direct crystallization, the greater will be the tendency for the enantiomorph to crystallize. It is preferred that this differential be at least 10°C. and not to exceed 60°C.

Other methods of forming supersaturated solutions may be used such as maintaining a constant temperature but changing the amount of salt-forming acid present by neutralization. This neutralization technique may also be used in conjunction with a temperature change. A further method may employ a change in pressure with temperature.

The amount of seed crystals employed will determine the efficiency of the direct crystallization. It is preferred that at least 5 g. of seed be added per liter of supersaturated solution. This may vary, however, to as high as 150 g. per liter or even more. The amount of seed also depends on the particle size of the seed crystals. If the amount added is small or the particles are large, the rate of crystallization is slow and therefore subject to contamination. Larger amounts or smaller particle size result in an increased rate of crystallization.

When a continuous process is used the preferred procedure is one that is carried out by preparing a saturated solution of the racemic mixture in separate crystallizing vessels containing seed crystals of the desired enantiomorph. Supersaturation of the solution is then performed and the particular enantiomorph crystallizes out. When this crystallization is carried out in series, the mother liquor from the first crystallization is continuously run into the next and its mother liquor is continuously recycled to a dissolving vessel feeding saturated solution into the crystallizing vessels. A further preferred continuous process is one in which a saturated solution stream is divided into two parts, each of which is used to prepare one of the enantiomorphs. The mother liquors are reunited and recycled to the dissolving step and additional racemic mixture is added to this dissolving step to maintain a saturated solution. The mother liquors of one enantiomorph may also be recycled to the dissolving step to form a saturated solution from which the remaining enantiomorph may be prepared.

If desired, when the direct crystallization is completed, the various protective groups on the hydroxy, hydrazino or acid moiety of the molecule may be removed hydrolytically or reductively by methods known in the art.

The seed crystals used in this invention may be prepared by the procedure outlined in pending application United States Serial No. 835,307, filed June 18, 1969, corresponding to Canadian Application Serial No. 85,145, filed June 10, 1970, now Canadian Patent 868,934.

With β-(3,4-dihydroxyphenyl)-α-hydrazinopropionic acid, the D-enantiomorph is isomerized in oxygen free alkaline solution to the racemate and recycled to the resolution.

The following are representative examples which show the novel process of this invention. They are to be construed as illustrations of this invention and not as limitations thereof.

EXAMPLE 1

A. Forty-five grams of DL-α-(3,4-dihydroxybenzyl)-α-hydrazinopropionic acid is dissolved in 115 ml. of 1 N hydrochloric acid at 45°C. The mixture is filtered and the saturated solution is then seeded at 45°C. with 5 g. of L-α-(3,4-dihydroxybenzyl)-α-hydrazinopropionic acid. The saturated solution is then cooled to 25°C. over thirty-five minutes and allowed to stand for one hour at 25°C. The separated material is then isolated by filtration, washed with two 15 ml. portions of water (25°C.) and dried *in vacuo* to obtain L-α-(3,4-dihydroxybenzyl)-α-hydrazinopropionic acid (m.p. 208°C., dec.).

B. The mother liquor from the preceding step (A) is combined with 5 g. of DL-α-(3,4-dihydroxybenzyl)-α-hydrazinopropionic acid and heated to 45°C. The mixture is

B

heated to 45°C. and filtered. The saturated solution is then treated with 4 g. of D-α-(3,4-dihydroxybenzyl)-α-hydrazinopropionic acid and cooled to 25°C. over one-half hour. The crystallized material is then isolated as above.

C. The mother liquor from the preceding step (B) is then recycled with 5 g. of DL-α-(3,4-dihydroxybenzyl)-α-hydrazinopropionic acid following the procedure of step (A) to obtain L-α-(3,4-dihydroxybenzyl)-α-hydrazinopropionic acid.

Example 2

When the above procedure of Example 1A is followed, but the conditions of Table I are substituted, the product obtained is L-α-(3,4-dihydroxybenzyl)-α-hydrazinopropionic acid.

Table I

(a) The DL mixture is dissolved in 20% aqueous methanol at 60°C.

(b) The acid used is 0.1 N hydrochloric acid.

(c) The saturated solution is seeded with 3.7 g. of L-enantiomorph and cooled to 15°C.

(d) The acid used is 0.1 N sulfuric acid.

(e) No acid is used.

(f) The seeded saturated solution is cooled while mildly stirred.

(g) The DL mixture is heated to 50°C. and cooled to 20°C.

Example 3

A vessel , A, is charged with 195 ml. of 0.1 N hydrochloric acid and 19 g. of DL-α-(3,4-dihydroxybenzyl)-α-hydrazinopropionic acid. This slurry is heated to 45°C.

with a water-bath and maintained at this temperature throughout the operation. A line from vessel A leads through a filter and divides into two lines which lead to vessels B and C. Vessels B and C are charged with 12 g. of DL-α-(3,4-dihydroxybenzyl)-α-hydrazinopropionic acid dissolved in 230 ml. of 0.1 N hydrochloric acid at 25°C. The solution is filtered to insure absence of suspended particles and 115 ml. of solution is added to vessel B and the remaining amount to vessel C. Vessels B and C are held at 25°C. during the operation. To vessel B is added 1.35 g. of L-α-(3,4-dihydroxybenzyl)-α-hydrazinopropionic acid and to vessel C is added 1.35 g. of D-α-(3,4-dihydroxybenzyl)-α-hydrazinopropionic acid.

The solution of vessel A is pumped at a rate of 2 ml. per minute to allow a flow of 1 ml. per minute to enter vessels B and C. From vessels B and C extend overflow lines which combine the overflow from vessels B and C and are returned to vessel A.

At regular intervals additional DL racemic mixture is added to vessel A to maintain a saturated solution. The D and L-isomers are removed at regular intervals and when necessary additional seed crystals are added.

Example 4

Two and one-half grams of DL-β-(3,4-dihydroxyphenyl)-α-hydrazinopropionic acid are dissolved in 50 ml. of distilled water at 75°C. The saturated solution is filtered hot, seeded with one-half gram of L-β-(3,4-dihydroxyphenyl)-α-hydrazinopropionic acid and then allowed to cool to room temperature over 1-1/2 hours. The mixture is then allowed to stand at room temperature for 1-1/2

hours longer, filtered, washed with cold distilled water (25°C.) and dried in vacuo to obtain L-β-(3,4-dihydroxyphenyl)-α-hydrazinopropionic acid (m.p. 197°C. (Brown's) dec.).

Example 5

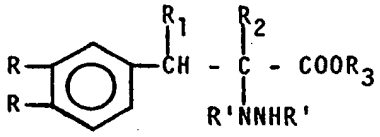
When the procedure of Example 1 is followed, but substituting the DL, D or L compounds of Table II for DL, D or L-α-(3,4-dihydroxybenzyl)-α-hydrazinopropionic acid, then the corresponding enantiomorph product is obtained.

Table II

β-(3,4-dihydroxyphenyl)-α-hydrazinopropionic acid
β-(3,4-dihydroxyphenyl)-α-hydrazinobutanoic acid
β-(3,4-dihydroxyphenyl)-α-methyl-α-hydrazinobutanoic acid
α-(3-hydroxybenzyl)-α-hydrazinopropionic acid
α-(4-hydroxybenzyl)-α-hydrazinopropionic acid
α-benzyl-α-hydrazinopropionic acid
methyl α-(3,4-dihydroxybenzyl)-α-hydrazinopropionate
methyl β-(3,4-dihydroxyphenyl)-α-hydrazinopropionate
α-(3,4-diacetyloxybenzyl)-α-N^1,N^2-diacetylhydrazinopropionic acid
α-(3,4-dibenzyloxybenzyl)-α-hydrazinopropionic acid
α-(3,4-dimethoxybenzyl)-α-hydrazinopropionic acid

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A process for obtaining a substantially pure enantiomorph of the formula:



where

R is hydrogen,
hydroxy,
loweralkyloxy,
benzyloxy or
loweralkanoyloxy;

R_1 and R_2 are hydrogen or
lower alkyl;

R_3 is hydrogen or
lower alkyl; and

R' is hydrogen or
loweralkanoyl,

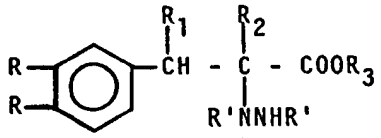
which comprises seeding a saturated solution of the racemic mixture with the desired enantiomorph.

2. A process according to Claim 1 where the saturated solution of the racemic mixture is formed with a polar solvent.

3. A process according to Claim 1 where the saturated solution is formed by preparing a saturated solution at a temperature of from about 40° to about 100°C. and cooling the resultant solution to about 5° to 40°C.

4. A process according to Claim 1 where the saturated solution comprises from 0 to 90% of the racemic mixture in the form of a salt.

5. A process for obtaining a substantially pure L-enantiomorph of the formula:



where

R is hydrogen,
hydroxy,
loweralkyloxy,
benzoyloxy or
loweralkanoyloxy;

R_1 and R_2 are hydrogen or
lower alkyl;

R_3 is hydrogen or
lower alkyl; and

R' is hydrogen or
loweralkanoyl,

which comprises seeding a saturated solution of the racemic mixture with substantially pure L-enantiomorph in crystalline form in a polar solvent which comprises at least 10% water and about 0-90% of the L-enantiomorph in the form of a salt, said salt being formed from a salt-forming acid having at least one acidic hydrogen whereby additional amounts of the L-enantiomorph crystallize in substantially pure form.

A1

6. A process according to claim 5 where the saturated solution of the racemic mixture is formed with water.

7. A process according to claim 5 where the saturated solution is formed by preparing a saturated solution at a temperature of from about 40° to about 100°C. and cooling the resultant solution to about 5° to 40°C.

8. A process according to claim 5 where the salt-forming acid is a non-oxidizing acid.

9. A process according to claim 5 where R is hydrogen or hydroxy, R_1 is hydrogen and R_2 is hydrogen or lower alkyl.

10. A process according to claim 5 where R is hydroxy, R_1 is hydrogen and R_2 is methyl, thus forming L-α-(3,4-dihydroxybenzyl)-α-hydrazinopropionic acid.

11. A process according to claim 5 where R is hydroxy, R_1 is hydrogen and R_2 is hydrogen, thus forming L-β-(3,4-dihydroxyphenyl)-α-hydrazinopropionic acid.

12. A process for resolving racemic α-(3,4-dihydroxybenzyl)-α-hydrazinopropionic acid which comprises, in combination, the steps of

(a) dissolving said racemate in a polar solvent containing 0 to 0.9 equivalent of a salt-forming acid per mole of said racemic mixture, said salt-forming acid having at least one acidic hydrogen with an ionization constant greater than 10^{-3}, the said polar solvent comprising at least 10% water, thus forming a saturated solution;

(b) separating any undissolved racemate;

(c) forming a supersaturated solution of the dissolved racemate in which from 0 to 90% of said hydrazino-acid compound is present as the salt of said salt-forming acid; and

(d) contacting portions of said supersaturated solution with each of the enantiomorphs in crystalline form, whereby additional amounts of each enantiomorph over the amount of said enantiomorph added as seed separate.

13. The process of continuously resolving racemic α-(3,4-dihydroxybenzyl)-α-hydrazinopropionic acid which comprises, in combination, the steps of

(a) forming a solution of said racemate in a polar solvent in which solution any salt-forming acid present is a water-soluble acid having at least one acidic hydrogen with an ionization constant greater than 10^{-3}, the said polar solvent comprising at least 10% water to form a substantially saturated solution of said racemate;

(b) continuously separating said saturated solution from undissolved racemate;

(c) continuously forming a supersaturated solution of the dissolved racemate having from 0 to 90% of said racemic compound present as the salt of said salt-forming acid;

(d) continuously contacting said supersaturated solution with one enantiomorph in crystalline form, whereby a portion of said enantiomorph separates from said supersaturated solution in crystalline form leaving a first mother liquor still supersaturated in the second enantiomorph;

(e) continuously separating said first mother liquor;

(f) continuously contacting said first mother liquor with said second enantiomorph in crystalline form, whereby a portion of said second enantiomorph separates in crystalline form, leaving a second mother liquor essentially racemic;

(g) continuously separating said second mother liquor and recycling it to the dissolving step;

(h) separating the crystallized enantiomorph from each of said crystallization steps, and returning the filtrate to the cycle;

(i) maintaining solid racemate in the dissolving step; and

(j) the said separating of saturated solution, of first mother liquor and of second mother liquor being made at rates adjusted to keep a balanced flow around the cycle.

14. The process of resolving racemic α-(3,4-dihydroxybenzyl)-α-hydrazinopropionic acid which comprises, in combination, the steps of

(a) dissolving said racemate in a polar solvent containing 0 to 0.9 equivalent of a salt-forming acid per mole of said racemic mixture, the said salt-forming acid being a water-soluble acid having at least one acidic hydrogen with an ionization constant greater than 10^{-3}, the said polar solvent comprising at least 10% water;

(b) separating any undissolved racemate;

(c) forming a supersaturated solution of the dissolved racemate having from 0 to 90% of said hydrazino-acid compound present as the hydrazine salt of said salt-forming acid;

(d) contacting said supersaturated solution with one of the enantiomorphs in crystalline form whereby addition of said enantiomorph is over the amount of said enantiomorph added as seed crystallizes leaving a first mother liquor still supersaturated in the second enantiomorph; and

(e) separating said first mother liquor from said crystals and contacting it with the said second enantiomorph in crystalline form, whereby a portion of said second enantiomorph separates from said first mother liquor leaving a second mother liquor essentially racemic.

15. The process of continuously resolving racemic α-(3,4-dihydroxybenzyl)-α-hydrazinopropionic acid which comprises, in combination, the steps of

(a) continuously forming a substantially saturated solution in a polar solvent comprising at least 10% water, said racemate in which any salt-forming acid present is a water-soluble nonamphoteric acid having at least one acidic hydrogen with an ionization constant greater than 10^{-3};

(b) continuously separating said saturated solution from undissolved racemate;

(c) continuously dividing said solution into two streams;

(d) continuously forming from each of said streams a supersaturated solution of dissolved racemate having from 0 to 90% of said hydrazino-acid compound in the form of the salt of said salt-forming acid;

(e) continuously contacting each of said streams with one of the enantiomorphs in crystalline form, the one supersaturated solution being contacted with one enantiomorph and the other with the other enantiomorph;

(f) continuously separating the mother liquors of each such crystallization from the crystallized enantiomorph;

(g) continuously combining said mother liquors and returning the combined stream to said dissolving step;

(h) maintaining solid undissolved racemate in said dissolving step; and

(i) the said separating of saturated solution and mother liquors being made at rates adjusted to keep the balanced flow around the cycle.

16. The process defined in Claims 12, 13 or 14 wherein the α-(3,4-dihydroxybenzyl)-α-hydrazinopropionic acid is replaced with β-(3,4-dihydroxyphenyl)-α-hydrazinopropionic acid and the product obtained is the corresponding enantiomorph.

17. The process defined in Claim 15 wherein the α-(3,4-dihydroxybenzyl)-α-hydrazinopropionic acid is replaced with β-(3,4-dihydroxyphenyl)-α-hydrazinopropionic acid and the product obtained is the corresponding enantiomorph.